Appendix E – Sensitivity analyses for modeling assumptions

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Sensitivity analyses for modeling assumptions

Table E1. Comparison of rate ratios and odds ratios for withdrawals due to adverse events: MTX-naive

Intervention	Rate ratio (95%CrI) (copied from Table 2 in manuscript)	Odds ratio (95%CrI)*
Methotrexate + abatacept (IV)	0.70 (0.21 to 2.35)	OR 0.71 (0.19 to 2.58)
Methotrexate + abatacept (sc)	0.97 (0.20 to 4.89)	OR 0.96 (0.18 to 4.99)
Methotrexate + adalimumab	1.21 (0.63 to 2.18)	OR 1.21 (0.61 to 2.21)
IM/sc Methotrexate + adalimumab	0.81 (0.07 to 8.06)	OR 0.73 (0.06 to 7.67)
Methotrexate + etanercept	0.80 (0.45 to 1.64)	OR 0.80 (0.44 to 1.70)
Methotrexate + golimumab (sc)	2.36 (0.67 to 9.67)	OR 2.35 (0.65 to 9.76)
Methotrexate + infliximab	2.53 (0.94 to 7.81)	OR 2.62 (0.91 to 7.88)
Methotrexate + rituximab	0.83 (0.22 to 3.01)	OR 0.85 (0.22 to 3.12)
Methotrexate + tocilizumab (4 mg/kg)	1.33 (0.46 to 3.77)	OR 1.35 (0.45 to 3.91)
Methotrexate + tocilizumab (8 mg/kg)	2.26 (0.82 to 6.38)	OR 2.33 (0.80 to 6.64)
Methotrexate + tofacitinib	0.90 (0.17 to 4.56)	OR 0.89 (0.16 to 4.66)
Methotrexate + azathioprine	5.79 (1.58 to 24.31)	OR 6.42 (1.66 to 29.49)
Methotrexate + cyclosporine	1.06 (0.37 to 2.38)	OR 1.04 (0.35 to 2.43)
IM/sc Methotrexate + cyclosporine	8.89 (0.98 to 139.30)	OR 7.97 (0.90 to 105.13)
Methotrexate + hydroxychloroquine/ chloroquine	1.35 (0.40 to 5.26)	OR 1.41 (0.41 to 5.09)
Methotrexate + sulphasalazine	1.31 (0.67 to 2.78)	OR 1.34 (0.67 to 2.97)
Methotrexate + sulphasalazine + hydroxychloroquine	0.67 (0.28 to 1.51)	OR 0.65 (0.26 to 1.53)
IM/sc Methotrexate	1.85 (0.56 to 6.69)	OR 1.77 (0.52 to 6.43)

*The standard deviation of the between study variability was 0.41 (0.08 to 0.96), similar to that for the primary analysis using rate ratios (see Appendix E, table 3E, below)

Appendix E – sensitivity analyses for modeling assumptions

Table E2. Comparison of rate ratios and odds ratios for withdrawals due to adverse events: MTX-IR

Intervention	Rate ratio (95%CrI) (copied from Table 2 in manuscript)	Odds ratio (95%CrI)*
MTX+ABAT (IV)	0.76 (0.44 to 1.30)	OR 0.77 (0.44 to 1.23)
MTX+ABAT (sc)	0.55 (0.28 to 1.03)	OR 0.54 (0.31 to 0.98)
MTX+ADA	1.44 (0.95 to 2.30)	OR 1.45 (0.97 to 2.29)
MTX+CTZ	1.42 (0.79 to 2.99)	OR 1.36 (0.70 to 2.59)
MTX+ETN	1.28 (0.56 to 2.92)	OR 1.32 (0.62 to 2.92)
MTX+GOL (sc)	1.02 (0.39 to 2.78)	OR 1.06 (0.34 to 2.92)
MTX+GOL (IV)	1.32 (0.36 to 6.31)	OR 1.41 (0.38 to 6.82)
MTX+IFX	1.62 (0.99 to 2.70)	OR 1.64 (1.00 to 2.74)
MTX+RTX	2.07 (0.74 to 6.45)	OR 2.36 (0.78 to 10.41)
MTX+TCZ (4 mg/kg)	1.63 (0.95 to 2.90)	OR 1.64 (0.98 to 2.82)
MTX+TCZ (8 mg/kg)	1.71 (1.01 to 2.84)	OR 1.74 (1.01 to 2.95)
MTX+TOFA	1.24 (0.74 to 2.26)	OR 1.22 (0.71 to 2.21)
MTX+CyA	3.27 (1.20 to 9.57)	OR 3.17 (1.18 to 10.94)
MTX+IMGold	4.12 (0.49 to 102.75)	OR 3.04 (0.33 to 57.74)
MTX+LEF	1.86 (0.74 to 4.68)	OR 1.89 (0.76 to 4.89)
MTX+SSZ+HCQ	1.82 (0.87 to 3.92)	OR 1.87 (0.91 to 3.91)

*The standard deviation of the between study variability was 0.18 (0.02 to 0.50), similar to that for the primary analysis using rate ratios (see Appendix E, table E3, below)

Table E3. Between study heterogeneity for primary analysis and sensitivity analyses for the choice of the prior distribution

		Prior used for the between study variability*		
Outome	**Treatment effect**	**Uninformative prior used for the main analysis Uniform (0,2) on standard deviation**	**Alternative uninformative prior Half-normal N(mu=0, sd=1) on standard deviation**	**Informative prior Normal (mu=-3.28, sd=0.73) distribution on log-variance**
MTX-naive				
ACR50	log(odds ratio)	0.19 (0.01 to 0.51)	0.21 (0.02 to 0.53)	0.16 (0.03 to 0.40)
Radiographic progression	standardized mean difference	0.14 (0.02 to 0.36)	0.14 (0.02 to 0.36)	0.12 (0.03 to 0.30)
WDAE	log(rate ratio)	0.39 (0.04 to 0.92)	0.37 (0.06 to 0.85)	0.23 (0.04 to 0.65)
MTX-IR				
ACR50	log(odds ratio)	0.24 (0.01 to 0.47)	0.24 (0.05 to 0.46)	0.19 (0.04 to 0.40)
Radiographic progression	standardized mean difference	0.23 (0.02 to 1.5)	0.23 (0.02 to 1.5)	0.11 (0.006 to 0.59)
WDAE	log(rate ratio)	0.16 (0.02 to 0.46)	0.15 (0.01 to 0.44)	0.14 (0.03 to 0.40)

Results shown are the standard deviation for the between study variability, median (95% credible interval).
*See statistical code below for the exact specification of the prior distributions. The informative priors were based on published studies; for the log(odds ratio) (ACR50 response) and log(rate ratio) (WDAE) we used the prior for a 'semi-objective outcome' for a meta-analysis of trials comparing pharmacologic agents (see Table 4 in Turner et al.)[1]; for the standardized mean difference (continuous outcome) we used the prior for an 'internal and external structure-related outcome' (see Table 3 in Turner et al.). [2]

Table E4. Comparison of treatment effects for ACR50 response using different prior distributions for the between-study variability: MTX-naive

Intervention	Uninformative prior used for the main analysis (copied from Table 2 in manuscript) OR (95% CrI)	Alternative uninformative prior OR (95% CrI)	Informative prior OR (95% CrI)
Methotrexate + abatacept (IV)	1.84 (1.01 to 3.42)	1.86 (0.98 to 3.49)	OR 1.85 (1.09 to 3.17)
Methotrexate + abatacept (sc)	1.98 (0.94 to 3.97)	1.95 (0.94 to 4.17)	OR 1.95 (1.02 to 3.76)
Methotrexate + adalimumab	2.10 (1.52 to 2.87)	2.11 (1.50 to 2.93)	OR 2.11 (1.59 to 2.78)
IM/sc methotrexate + adalimumab	2.22 (0.80 to 6.06)	2.18 (0.80 to 6.32)	OR 2.26 (0.90 to 5.64)
Methotrexate + certolizumab	1.49 (0.83 to 2.68)	1.50 (0.81 to 2.78)	OR 1.50 (0.90 to 2.51)
Methotrexate + etanercept	3.00 (2.02 to 4.59)	3.01 (1.97 to 4.62)	OR 3.04 (2.13 to 4.38)
Methotrexate + golimumab (sc)	1.33 (0.68 to 2.59)	1.32 (0.67 to 2.67)	OR 1.35 (0.75 to 2.46)
Methotrexate + infliximab	2.03 (1.30 to 3.77)	2.08 (1.28 to 3.95)	OR 2.00 (1.30 to 3.41)
Methotrexate + rituximab	2.42 (1.30 to 4.42)	2.41 (1.28 to 4.53)	OR 2.43 (1.41 to 4.23)
Methotrexate + tocilizumab (4 mg/kg)	1.66 (0.95 to 2.92)	1.66 (0.91 to 2.97)	OR 1.66 (1.02 to 2.67)
Methotrexate + tocilizumab (8 mg/kg)	1.91 (1.09 to 3.36)	1.90 (1.06 to 3.37)	OR 1.89 (1.17 to 3.08)
Methotrexate + tofacitinib	3.04 (1.05 to 9.37)	3.09 (1.04 to 9.22)	OR 2.98 (1.12 to 8.33)
Methotrexate + cyclosporine	1.72 (0.86 to 3.36)	1.76 (0.86 to 3.41)	OR 1.76 (0.95 to 3.38)
IM/sc Methotrexate + cyclosporine	1.57 (0.44 to 6.01)	1.60 (0.41 to 5.61)	OR 1.65 (0.48 to 5.76)
Methotrexate + hydroxychloroquine/ chloroquine	0.78 (0.23 to 2.90)	0.84 (0.21 to 2.90)	OR 0.82 (0.24 to 2.67)
Methotrexate + sulphasalazine	1.10 (0.41 to 2.78)	1.10 (0.43 to 2.86)	OR 1.10 (0.41 to 2.74)
Methotrexate + sulphasalazine + hydroxychloroquine	2.32 (1.17 to 4.79)	2.36 (1.13 to 4.99)	OR 2.39 (1.24 to 4.55)
IM/sc Methotrexate	1.13 (0.59 to 2.16)	1.13 (0.58 to 2.22)	OR 1.15 (0.64 to 1.97)

See statistical code below for the exact specification of the prior distributions. The informative priors were based on published studies; for the log(odds ratio) (ACR50 response) and log(rate ratio) (WDAE) we used the prior for a 'semi-objective outcome' for a meta-analysis of trials comparing pharmacologic agents (see Table 4 in Turner et al.)[1]; for the standardized mean difference (continuous outcome) we used the prior for an 'internal and external structure-related outcome' (see Table 3 in Turner et al.). [2]

Table E5. Comparison of treatment effects for ACR50 response using different prior distributions for the between-study variability: MTX-IR

Intervention	Uninformative prior used for the main analysis (copied from Table 2 in manuscript) OR (95% CrI)	Alternative uninformative prior OR (95% CrI)	Informative prior OR (95% CrI)
MTX + abatacept (IV)	3.81 (2.80 to 5.33)	OR 3.84 (2.77 to 5.36)	3.83 (2.86 to 5.11)
MTX + abatacept (sc)	4.16 (2.72 to 6.53)	OR 4.16 (2.76 to 6.53)	4.15 (2.86 to 6.11)
MTX + adalimumab	4.37 (3.38 to 5.89)	OR 4.41 (3.41 to 5.87)	4.35 (3.41 to 5.62)
MTX + etanercept	12.31 (5.76 to 30.78)	OR 12.57 (5.71 to 30.33)	12.26 (6.16 to 27.19)
MTX + golimumab (sc)	4.49 (2.57 to 8.01)	OR 4.56 (2.63 to 8.13)	4.51 (2.62 to 8.02)
MTX + golimumab (IV)	3.58 (1.79 to 7.25)	OR 3.55 (1.77 to 7.34)	3.54 (1.92 to 6.74)
MTX + infliximab	3.46 (2.46 to 5.00)	OR 3.47 (2.42 to 5.02)	3.47 (2.50 to 4.84)
MTX + rituximab	3.59 (2.18 to 6.27)	OR 3.71 (2.20 to 6.37)	3.75 (2.28 to 6.15)
MTX + tocilizumab (4 mg/kg)	2.57 (1.42 to 4.56)	OR 2.61 (1.44 to 4.46)	2.62 (1.52 to 4.40)
MTX + tocilizumab (8 mg/kg)	4.16 (2.46 to 6.85)	OR 4.17 (2.47 to 6.91)	4.27 (2.59 to 6.67)
MTX + tofacitinib	5.42 (3.31 to 9.01)	OR 5.37 (3.32 to 8.96)	5.40 (3.44 to 8.52)
MTX + hydroxychloroquine/ chloroquine	8.94 (2.18 to 46.14)	OR 9.23 (1.93 to 42.12)	9.15 (2.32 to 38.66)
MTX + IM Gold	16.34 (2.03 to 553.42)	OR 14.68 (1.88 to 328.46)	13.44 (1.82 to 508.29)
MTX + leflunomide	5.69 (2.23 to 16.27)	OR 5.77 (2.26 to 16.07)	5.71 (2.29 to 15.33)
MTX + sulphasalazine	2.50 (0.49 to 13.76)	OR 2.60 (0.44 to 13.24)	2.44 (0.49 to 11.47)
MTX + sulphasalazine + hydroxychloroquine	10.51 (4.46 to 30.81)	OR 10.83 (4.15 to 29.56)	10.62 (4.83 to 26.44)

See statistical code below for the exact specification of the prior distributions. The informative priors were based on published studies; for the log(odds ratio) (ACR50 response) and log(rate ratio) (WDAE) we used the prior for a 'semi-objective outcome' for a meta-analysis of trials comparing pharmacologic agents (see Table 4 in Turner et al.)[1]; for the standardized mean difference (continuous outcome) we used the prior for an 'internal and external structure-related outcome' (see Table 3 in Turner et al.). [2]

References

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